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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,718	GUO, BAOCHUAN	
	Examiner	Art Unit	
	Dan-Sung C. Cho	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-22 and 24-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22 and 24-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 2/26/2007. Currently, claims 18-22, 24-36 and newly added claims 37-39 are pending. Amendment to claim 24 and new amendments 37-39 in a paper filed on 2/26/2007 is acknowledged.

2. All the amendment and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are reiterated or newly applied as necessitated by the amendment. They constitute the complete set being presently applied to the instant Application.

All rejections are maintained. Response to Applicant's arguments follows. This action is **FINAL.**

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 24, 27-36 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Landers (herein referred to as Landers, US Patent US 6,844,154 B2, Jan. 18, 2005, filed Mar. 30, 2001).

With regard to claims 24 reciting "...non-enriched allelic variant is present, the enriched allelic variant is present in an amount that is from 1.5 to 100 times greater than the amount of the non-enriched allelic variant...", Landers teaches obtaining an enriched nucleic acid fraction that contains more of one allelic variant of a haplotype of two SNPs by hybridization to a probe on a surface that is specific for one particular allele of one SNP of a haplotype (Figure 1, 2, 3A and 3B; column 2, lines 38-63; column 3, lines 18-19 and 47-68; column 9, lines 22-32 and 45-51; column 16, lines 30-50). Landers teaches that this complex is hybridized with a probe that specifically binds to a particular allele of the other SNP of the haplotype and genotyping involves detecting a signal from this probe which indicates the presence of particular alleles in both SNPS of the haplotype (see Figure 1, 2, 3A and 3B; column 2, lines 38-63; column 9, lines 45-51; column 16, lines 30-50; column 26, lines 60-67). Landers teaches that the presence of a second allelic-variant haplotype, which would be at a lower level in the enriched fraction of the first haplotype, can be detected by analogous hybridization with a probe on a surface that specifically binds to a different allele of the first SNP of the haplotype and detection with a probe that specifically binds to an allele of the

second SNP of the haplotype (Figures 1, 2, 3A and 3B; column 26, lines 60-67; column 27, lines 1-8).

With regard to claims 32 reciting "...the enriched allelic variant is present in an amount that is from 2 to 30 times greater than the amount of the non-enriched allelic variant....", Landers teaches enrichment of nucleic acid fraction that contains more of one allelic variant of a haplotype of two SNPs by hybridization to a probe on a surface that is specific for one particular.

With regard to claims 33 reciting "...the nucleic acid fraction contains nucleic acid molecules that do not hybridize to the allele-specific hybridization probe...:, Landers teaches purification or isolation of ASO-captured allele by "separating the labeled nucleic acid samples into single nucleic acid molecules, detecting the presence of absence of the first, second, third and fourth labeled probes" (column 4, lines 5-9). Landers further teaches a bi-phasic allele specific oligonucleotide hybridization techniques where (1) a SNP1 allele –specific oligonucleotide (ASO) is used to capture a SNP1/nucleic acid sample complex; (2) Excess un-hybridized DNA is removed (column 14 lines 45-65).

With regard to claims 36 reciting "...the enriched allelic variant is present in an amount that is from 3 to 6 times greater than the amount of the non-enriched allelic variant...", Landers teaches obtaining an enriched nucleic acid fraction that contains more of one allelic variant of a haplotype of two SNPs by hybridization to a probe on a surface that is specific for one particular.

With regard to claims 27 and 28 reciting "...the subject is diploid" and "the sample is a nucleic acid...", Landers teaches using RNA, cDNA or gnomic DNA which are diploid (claims 20-22).

With regard to claims 29 reciting "...the allele-specific hybridization probe is attached to a solid support or to a first binding molecule that is capable of binding to a second binding molecule that is attached to a solid support, and wherein the nucleic acid sample and the allele-specific hybridization probe are contacted under hybridization conditions that allow the allele-specific hybridization probe to preferentially hybridize with one allele of the first selected SNP site.....", Landers teaches using direct or indirect avidin-biotin coupling techniques (column 9 lines 4-21).

With regard to claims 30 reciting "...the allele-specific hybridization probe is attached to a solid support or to a first binding molecule that is capable of binding to a second binding molecule that is attached to a solid support, and wherein the nucleic acid sample and the allele-specific hybridization probe are contacted under hybridization conditions that allow the allele-specific hybridization probe to preferentially hybridize with one allele of the first selected SNP site.....", Landers teaches using direct or indirect avidin-biotin coupling techniques (column 9 lines 4-21; column 18 lines 44-61).

With regard to claims 31 reciting "...the first binding molecule is biotin streptavidin and said second binding molecule is streptavidin or biotin.....", Landers teaches using biding partners such as avidin, biotin, streptavidin, antibody and antigen (column 9 lines 4-21; column 18 lines 44-61).

With regard to claims 34 reciting "... the allele-specific hybridization probe is an oligonucleotide, a peptide nucleic acid or a locked nucleic acid.....", Landers teaches using oligonucleotide (claims1, 2, 7, 9, 10, 12, where ASO is Allele-Specific Oligonucleotide).

With regard to claims 35 reciting "...allele-specific hybridization probe is an oligonucleotide that is attached to a first binding molecule and the nucleic acid sample is contacted with both the allele-specific hybridization probe and a competitor oligonucleotide that hybridizes to the other allele of the first selected SNP site and that is not attached to the first binding molecule", Landers teaches that cold competitor oligos that hybridize to the other allele of the SNP site and not attached to a binding partner such as biotin or avidin (claim 15, column 27, lines 10-24 of Landers).

Landers does not specifically teach the range of enrichment after ASO-mediated selection. However given the method steps used by Landers which appear to be the method steps of the instant application the range of enrichment would inherently be the same.

However, per MPEP 2144.05, where the general conditions of the claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation and it is the normal desire of scientists and artisans to improve on what is already generally known. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made improve the method of haplotype analysis taught by Landers through routine experimentation to provide optimal or workable ranges, such as where the enriched allelic variant is present in an

amount that is from 1.5 to 100 times or more specifically 2-30, greater than the amount of the non-enriched allelic variant. The ordinary artisan would have been motivated to have enriched the sample 2-30 times to allow increased sensitivity to ensure results of haplotype analysis did not show false results.

Response to Arguments

5. The response traverses the rejection. Applicant's arguments filed 2/26/2007 have been fully considered but they are not deemed persuasive. The response asserts on page 6, para 2-3 that Landers teaches in all examples that the entire nucleic acid having the SNP sites of interest is first subjected to PCR amplification and then the amplified nucleic acid is subjected to allele-specific hybridization. The response further asserts on page 6, para 3, lines 5-6, that Landers do not teach or suggest that the method could be practiced without an initial amplification of the original nucleic acid sample.

This argument has been thoroughly reviewed but was not found persuasive. First, the instant claims are drawn to a method "comprising" of the steps in the claim 24 and do not prohibit a step before the ASO step recited. Second, the specification does not limit interpretation of original nucleic acid as one that has not been amplified (col 11, para 4, lines 40-41 and 30-32; col 10, lines 50-59; col 11, para 4). Third, Landers teaches use of the PCR generated reduced complexity genome (RCG) but also teaches native RCG where size fractionation is instead used to produce the RCG (col 11, lines 40-41 and 30-32). Landers teaches use of "DNA fragment" which is obtained from a genome at any point along the genome and encompassing any sequence of

nucleotides. The DNA fragments of the invention can be generated according to any one of two types mechanisms, and thus there are two types of RCGs, PCR-generated RCGs and native RCGs" (col. 11, lines 35-41).

The response asserts on page 6, para 2, lines 9-11, that the instant specification teaches use of an "original nucleic acid" samples that have not been subjected to amplification and cites paragraphs 34-38. This argument and the specification have been thoroughly reviewed. However, the specification does not limit interpretation of this phrase as one that has not been amplified. The amendment to claim 24 to recite "an original nucleic acid" is acknowledged. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore Landers teaches all the limitations of the instant claims and the rejections of the instant claims on the record are maintained. For these reasons and the reasons already made of record, the rejection is maintained.

Claim Rejections - 35 USC § 103 (a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 18-22 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landers (US Patent US 6,844,154 B2, Jan. 18, 2005, filed Mar. 30,

2001) in view of Sorenson (herein referred to as Sorenson, US Patent 6,020,124, 02/2000).

With regard to Claim 18 reciting "...preferentially extracting one of said two allelic variants from an original nucleic acid sample comprising said two allelic variants of said chromosome or chromosomal fragment to provide an enriched sample in which the level of the preferentially extracted allelic variant is from 2 to 30 times greater than the level of the allelic variant that is not preferentially extracted from the sample by contacting said chromosome chromosomal fragment with an allele-specific hybridization probe ...", Landers teaches obtaining an enriched nucleic acid fraction that contains more of one allelic variant of a haplotype with ASO (Figure 1, 2, 3A and 3B; column 2, lines 38-63; column 3, lines 18-19 and 47-68; column 9, lines 22-32 and 45-51; column 16, lines 30-50). Landers also teaches that this complex is hybridized with a probe that specifically binds to a particular allele of the other SNP of the haplotype and genotyping involves detecting a signal from this probe which indicates the presence of particular alleles in both SNPS of the haplotype (see Figure 1, 2, 3A and 3B; column 2, lines 38-63; column 9, lines 45-51; column 16, lines 30-50; column 26, lines 60-67). Landers teaches that the presence of a second allelic-variant haplotype, which would be at a lower level in the enriched fraction of the first haplotype, can be detected by analogous hybridization with a probe on a surface that specifically binds to a different allele of the first SNP of the haplotype and detection with a probe that specifically binds to an allele of the second SNP of the haplotype (Figures 1, 2, 3A and 3B; column 26, lines 60-67; column 27, lines 1-8).

Landers does not teach a method of haplotyping which involves amplifying the nucleic acids in the enriched nucleic acid fraction prior to identifying the alleles of interest.

However, Sorenson teaches that prior to determining the alleles present in a particular nucleic acid, the nucleic acid sample can be amplified with a common amplification step by PCR to amplify wild-type and mutant forms of the DNA to increase the amount of DNA from which the mutant allele can be detected (see column 2, lines 35-39 of Sorenson). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of haplotype identification taught by Landers to include PCR amplification of the nucleic acids in the enriched nucleic acid fraction prior to identifying the alleles of interest by using an amplification that would amplify all of the allelic variants in the same proportion in view of the teachings of Sorenson.

The ordinary artisan would have been motivated to improve the method of haplotype identification taught by Landers to include PCR amplification of the nucleic acids in the enriched nucleic acid fraction prior to identifying the alleles of interest by using an amplification that would amplify all of the allelic variants in the same proportion because Sorenson teaches that a common amplification step prior to specific allele identification increases the amount of DNA from which mutant alleles can be detected.

Landers in view of Sorenson does not teach methods of haplotype analysis in which the level of the preferentially extracted allelic variant is from 2 to 30 times greater than the level of the allelic variant that is not preferentially extracted.

However, per MPEP 2144.05, where the general conditions of the claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation and it is the normal desire of scientists and artisans to improve on what is already generally known. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made improve the method of haplotype analysis taught by Landers in view of Sorenson through routine experimentation to provide optimal or workable ranges, such as the level of the preferentially extracted allelic variant is from 2 to 30 times greater than the level of the allelic variant that is not preferentially extracted (claim 18) in view of Landers.

The ordinary artisan would have been motivated to improve the method of haplotype analysis taught by Landers in view of Sorenson through routine experimentation to provide optimal or workable ranges, such as where the level of the preferentially extracted allelic variant is specifically from 2 to 30 times greater than the level of the non-preferentially extracted for the purpose of obtaining the optimal range to practice the method of haplotyping taught by Landers in view of Sorenson.

With regard to claim 19 reciting "...one of said allelic variants is preferentially extracted from said original nucleic acid sample by a solid phase extraction technique...", Landers teaches obtaining nucleic acid fraction that contains more of one allelic variant of a haplotype of two SNPs by using allele-specific oligonucleotide hybridization technique and solid phase extraction (claims 1-3, 12 and 16; Figure3; column 26, lines 34-45). Landers teaches that the presence of a second allelic-variant

haplotype, which would be at lower level in the enriched fraction of the first haplotype, can be detected by analogous hybridization with a probe on a solid support that specifically binds to a different allele of the first SNP of the haplotype and detection with a probe that specifically binds to an allele of the second SNP of the haplotype (claims 1-3, 12, and 16., see Figures 3 and 5 and column 26, lines 60-67 and column 27, lines 1-8).

With regard to Claim 20 reciting "...allele-specific hybridization probe is an oligonucleotide that is attached to a first binding molecule, and said solid phase extraction technique also employs a competitor oligonucleotide that hybridizes to the other allele of the heterozygotes SNP site and that is not attached to the first binding molecule ...", Landers teaches that cold competitor oligos that hybridize to the other allele of the SNP site that is being detected can be added with the labeled allele-specific probes (claim 15, column 27, lines 10-24 of Landers).

With regard to Claim 21 reciting "...the genotypes of the chromosome or chromosomal fragments are determined before one allelic variant of the chromosome or chromosomal fragments is extracted from the original nucleic acid sample. ...", Landers teaches purification or isolation of ASO-captured allele by "separating the labeled nucleic acid samples into single nucleic acid molecules, detecting the presence of absence of the first, second, third and fourth labeled probes" (column 4, lines 5-9). Landers further teaches a bi-physic allele specific oligonucleotide hybridization techniques where (1) a SNP1 allele –specific oligonucleotide (ASO) is used to capture a SNP1/nucleic acid sample complex; (2) Excess un-hybridized DNA is removed to purify

the first SNP1 allele-specific DNA; (3) SNP2 is analyzed. (column 14 lines 45-65). Landers further teaches a method in which after the first SNP has been identified, the DNA molecules containing the first allele are in a separate container from the DNA samples containing the second allele (column 16 lines 30-34).

With regard to claim 22 reciting "...the amount of the enriched allelic variant in the enriched nucleic acid fraction is from 3 to 10 times greater than the amount of the non-enriched allelic variant in the nucleic acid sample....", Landers teaches purification or isolation of ASO-captured allele (column 4, lines 5-9). Sorenson teaches that prior to determining the alleles present in a particular nucleic acid, the nucleic acid sample can be amplified with a common amplification step by PCR to amplify wild-type and mutant forms of the DNA to increase the amount of DNA from which the mutant allele can be detected (see column 2, lines 35-39 of Sorenson). Landers in view of Sorenson do not teach methods of haplotype analysis in which the level of the preferentially extracted allelic variant is from 3 to 10 times greater than the level of the allelic variant that is not preferentially extracted.

However, per MPEP 2144.05, where the general conditions of the claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation and it is the normal desire of scientists and artisans to improve on what is already generally known. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made improve the method of haplotype analysis taught by Landers in view of Sorenson through routine experimentation to provide optimal or workable ranges, such as the level of the

preferentially extracted allelic variant is from 3 to 10 times greater than the non-enriched allele.

The ordinary artisan would have been motivated to improve the method of haplotype analysis taught by Landers in view of Sorenson through routine experimentation to provide optimal or workable ranges, such as where the level of the preferentially extracted allelic variant is from 3 to 30 times greater than the level of the non-enriched allele for the purpose of obtaining the optimal range to practice the method of haplotyping taught by Landers in view of Sorenson.

With regard to claim 25 reciting "...the nucleic acid fraction is combined under polymerase chain reaction amplification conditions with one or more primer sets, ...", Landers teaches purification or isolation of ASO-captured allele (column 4, lines 5-9). Sorenson teaches that prior to determining the alleles present in a particular nucleic acid, the nucleic acid sample can be amplified with a common amplification step by PCR to amplify wild-type and mutant forms of the DNA to increase the amount of DNA from which the mutant allele can be detected (see column 2, lines 35-39 of Sorenson).

With regard to Claim 26 reciting "...primer sets do not hybridize to portions of the nucleic acid that flank the first selected SNP site....", Landers teaches obtaining an enriched nucleic acid fraction with ASO (Figure 1, 2, 3A and 3B; column 2, lines 38-63; column 3, lines 18-19 and 47-68; column 9, lines 22-32 and 45-51; column 16, lines 30-50). Sorenson teaches PCR amplification in an allele-specific manner to distinguish a normal gene to sequence from a mutated gene sequence (see column 2, lines 30-34 of Sorenson). Therefore, it would have been prima facie obvious to one of ordinary skill

in the art at the time the invention was made to improve the method of haplotype identification taught by Landers to include PCR amplification of the nucleic acids in the enriched nucleic acid fraction with allele-specific primer sets that do not hybridize to portions of the nucleic acid that flank the first selected SNP site in view of the teachings of Sorenson to PCR amplification selectivity and sensitivity to ensure results of haplotype analysis did not show false results.

Response to Arguments

7. The response traverses the rejection. Applicant's arguments filed 2/26/2007 have been fully considered but they are not deemed persuasive. The response asserts on page 7, para 2, lines 3-5 that the examiner misconstrued the references because both Landers and Sorenson teach amplification of the original nucleic acid sample prior to any hybridization for enrichment.

This argument has been thoroughly reviewed but was not found persuasive. First, the instant claims are drawn to a method "comprising" of the steps in the claim 24 and do not prohibit a step before the ASO step recited. Second, the specification does not limit interpretation of original nucleic acid as one that has not been amplified (col 11, para 4, lines 40-41 and 30-32; col 10, lines 50-59; col 11, para 4). Third, Landers teaches use of the PCR generated reduced complexity genome (RCG) but also teaches native RCG where size fractionation is instead used to produce the RCG (col 11, lines 40-41 and 30-32). Landers teaches use of "DNA fragment" which is obtained from a genome at any point along the genome and encompassing any sequence of

nucleotides. The DNA fragments of the invention can be generated according to any one of two types mechanisms, and thus there are two types of RCGs, PCR-generated RCGs and native RCGs" (col. 11, lines 35-41).

The response asserts on page 7, para 3, lines 1-5, that the amplification in the instant application and what Landers and Sorenson teach are different because only the instant application teach amplification wherein the enrichment selectively increases the ratio of enriched molecules to non-enriched molecules. This argument has been thoroughly reviewed but was not found persuasive because as amplifications Landers and Sorenson also teach a method of amplifying a region of genomic DNA so that the amplified DNA molecules are enriched and the ratio of amplified DNA to unamplified DNA is selectively increased (See Landers et al., col 22, lines 33-46; and Sorenson et al., Experiment C).

The response asserts on page 7, para 3, lines 5-7, that instant application claims 18 and 24 recite that the nucleic acid sample is original and that it is not amplified. Claim 18 in line 17 and 20 recite "original nucleic acid". This argument has been thoroughly reviewed but was not found persuasive because claim 18 recites "identifying the alleles of the SNPs of interest that are present at higher levels in the amplified enriched sample" in line 15-16 and "identifying the alleles of the SNPs of interest that are present at lower levels in the amplified enriched sample". The amended claim 24 recites "combining an original nucleic acid" with allele specific probe. Landers teaches a method wherein allele specific oligonucleotide (ASO)-mediated capture of nucleic acid sample (col 2, lines 39-50). The nucleic acid sample that are used can be of any type of

nucleic acid, amplified or the original unamplified as noted above. Sorenson teaches amplification steps. Therefore Landers and Sorenson teach a method wherein nucleic acid is captured with ASO and then amplified as set forth above and teach all the limitations of the instant claim.

The response asserts on page 7, para 3, lines 7-12 that neither Landers nor Sorenson makes any mention or suggestion of the desirability of first enriching the original nucleic acid sample before any amplification. This argument has been thoroughly reviewed but was not found persuasive because the instant claims are drawn to a haplotyping method "comprising" of the recited steps. Landers teaches a method wherein allele specific oligonucleotide (ASO)-mediated capture on a nucleic acid sample of any type (col 2, lines 39-50). Sorenson teaches amplification steps. Therefore Landers and Sorenson teach a method wherein a nucleic acid is first captured with ASO and then amplified as set forth above and teach all the limitations of the instant claim.

The response asserts on page 7, para 3, lines 12-18 that neither Landers nor Sorensen makes any mention or suggestion of the desirability of using primer sets that can flank only one SNP and provides no motivation to modify any teachings regarding pre-enrichment amplification of all SNPs within a target region and to eliminate the amplification of the original sample prior to any hybridization or enrichment. As noted above, Landers teaches ASO capture of a target nucleic acid from any nucleic acid including the "original" unamplified DNA. After the pre-enrichment of a specific allele of the SNP, Landers teach PCR amplification of the specific pre-enriched allele of the SNP

site and therefore teaches all the limitations of the claim. For these reasons and the reasons already made of record, the rejection is maintained.

New Rejection necessitated by amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 38-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Upon review of the specification, the specification does not appear to provide support for recitation of "wherein the one or more primer sets do not flank the first SNP site" in claim 38 and "wherein the step of PCR amplification is carried out with one or more primer set that do not flank the first SNP site". The specification on page 14, para 48, lines 7 and 16 discloses use of one or more primer sets for SNP1 and SNP2 after enrichment of a region of interest, the specification does not limit, however, that the second primer set that flanks the SNP2 site, flanks only the second SNP site and not the first SNP site. These new claims, therefore, constitute new matter.

Claim Rejections - 35 USC § 103 (a)

9. Claims 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landers (US Patent US 6,844,154 B2, Jan. 18, 2005, filed Mar. 30, 2001) in view of Castaldo (Castaldo et al., 1999, Clinical Chemistry 45: 957-962).

With regard to Claim 37, Landers teaches obtaining an enriched nucleic acid fraction that contains more of one allelic variant of a haplotype with ASO (Figure 1, 2, 3A and 3B; column 2, lines 38-63; column 3, lines 18-19 and 47-68; column 9, lines 22-32 and 45-51; column 16, lines 30-50). Landers also teaches that this complex is hybridized with a probe that specifically binds to a particular allele of the other SNP of the haplotype and genotyping involves detecting a signal from this probe which indicates the presence of particular alleles in both SNPS of the haplotype (see Figure 1, 2, 3A and 3B; column 2, lines 38-63; column 9, lines 45-51; column 16, lines 30-50; column 26, lines 60-67). Landers teaches that the presence of a second allelic-variant haplotype can be detected by analogous hybridization with a probe on a surface that specifically binds to a different allele of the first SNP of the haplotype and detection with a probe that specifically binds to an allele of the second SNP of the haplotype (Figures 1, 2, 3A and 3B; column 26, lines 60-67; column 27, lines 1-8).

Landers does not teach a method of haplotyping wherein the SNP site of the extraction step is a first SNP site and PCR amplification is carried out with one or more primer sets that flank at least a second SNP site within or near the target sequence or wherein the one or more primer sets do not flank the first SNP site or wherein the step of PCR amplification is carried out with one or more primer sets that do not flank the first SNP site.

However, with regard to claim 37, Castaldo teaches a method wherein five CF gene mutations are analyzed in a multiplex PCR by using primers specific for single SNP. For example Castaldo teaches use of forward primer and reverse primer for exon 17b SNP L1065 that does not amplify the G1244E exon 20 SNP site (Table 1) Because ASO dot blot is used after PCR each PCR amplification is directed to single SNP sites (Figure 3). The two SNP sites are near to each other because they are on the same CFTR gene. Castaldo teaches that the method of haplotyping using the multiplexed PCR wherein single SNP region is amplified represents a step forward in a strategy to eradicate the disease associated with the gene (page 962, left col., para 1, lines 4-8).

With regard to claims, 38 and 39, Castaldo teaches a method wherein second PCR primer set do not flank the first SNP site (Table 1). For example, the primer sets for the intron 5 do not flank the exon 20 SNP primers (Table 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of haplotype identification taught by Landers to include PCR amplification of the nucleic acids in the enriched nucleic acid fraction with allele-specific primer sets wherein the SNP site of the extraction step is a first SNP site and PCR amplification is carried out with one or more primer sets that flank at least a second SNP site within or near the target sequence or wherein the one or more primer sets do not flank the first SNP site or wherein the step of PCR amplification is carried out with one or more primer sets that do not flank the first SNP site.

The ordinary artisan would have been motivated to improve the method of haplotype identification taught by Landers to include PCR amplification of the nucleic acids in the enriched nucleic acid fraction by using an amplification that would amplify individual SNP site separately as taught by Castaldo because Castaldo teaches a SNP genotyping and haplotyping methods which can help identify disease-related genotypes and haplotypes for development of genotype- and haplotype-based disease diagnostic tests.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dan-Sung Cho whose telephone number is (571) 272-9933. The examiner can normally be reached on Mon-Fri, 7-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Dan-Sung C. Cho
Examiner
AU 1634
5/14/07

JEHANNE SITTON
PRIMARY EXAMINER
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